Nevirapine (NVP, Viramune)

For additional information see Drugs@FDA:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Tablets: 200 mg, extended release 400 mg
Suspension: 10 mg/mL

Dosing Recommendations

Neonate/infant dose:

Neonate/infant dose (age ≤14 days):

See Perinatal Guidelines for information on use of NVP for prophylaxis of mother-to-child transmission (MTCT) of HIV. Treatment dose is not defined for infants age ≤14 days.

Pediatric dose (age ≥15 days):

(See note below about initiation of therapy.)

Age <8 years:
200 mg/m^2 of body surface area/dose (maximum dose 200 mg) twice daily.

Age ≥8 years: 120–150 mg/m^2 of body surface area/dose (maximum dose 200 mg) twice daily.

When adjusting the dose for a growing child, the mg dose need not be decreased as the child reaches 8 years; rather, the mg dose is left static to achieve the appropriate mg-per-m^2 dosage as the child grows, as long as there are no untoward effects.

Note: NVP is initiated at a lower dose and increased in a stepwise fashion to allow induction of cytochrome P (CYP) 450 metabolizing enzymes, which results in increased clearance of the drug. The occurrence of rash is diminished by this stepwise increase in dose. Initiate therapy with the age-appropriate dose once daily for the first 14 days of therapy. If there is no rash or untoward effect, at 14 days of therapy increase to the age-appropriate dose administered twice daily. The total daily dose should not exceed 400 mg.

Adolescent/adult dose:

200 mg twice daily.

Note: Initiate therapy with 200 mg given once daily

Selected Adverse Events

- Rash, including Stevens-Johnson syndrome (SJS)
- Symptomatic hepatitis, including fatal hepatic necrosis
- Severe systemic hypersensitivity syndrome with potential for multisystem organ involvement and shock

Special Instructions

- NVP can be given without regard to food.
- NVP-associated skin rash usually occurs within the first 6 weeks of therapy. If rash occurs during the initial 14-day lead-in period, do not increase NVP dose until rash resolves (see Major Toxicities).
- If NVP dosing is interrupted for more than 7 days, NVP dosing should be restarted with once-daily dosing for 14 days, followed by escalation to the full, twice-daily regimen.
- Most cases of NVP-associated hepatic toxicity occur during the first 12 weeks of therapy; frequent clinical and laboratory monitoring, including liver function tests (LFTs), is important during this time period. However, about one-third of cases occurred after 12 weeks of treatment, so continued periodic monitoring of LFTs is needed. In some cases, patients presented with nonspecific prodromal signs or symptoms of hepatitis and rapidly progressed to hepatic failure. Patients with symptoms or signs of hepatitis should have LFTs performed. NVP should be permanently discontinued and not restarted in patients who develop clinical hepatitis or hypersensitivity reactions (HSRs).
- Shake NVP suspension well and store at room temperature.

for the first 14 days. Increase to 200 mg administered twice daily if there is no rash or other untoward effects.

400 mg extended release once daily (not approved for use in children).

Note: Initiate therapy with 200-mg immediate-release tablet given once daily for the first 14 days. Increase to 400 mg administered once daily if there is no rash or other untoward effects. In patients already receiving full-dose immediate-release NVP, extended-release tablets can be used without the 200-mg lead-in period. Patients must swallow NVP extended-release tablets whole. They must not be chewed, crushed, or divided. Patients must never take more than one form of nevirapine at the same time.

NVP in combination with lopinavir/ritonavir (LPV/r):
A higher dose of LPV/r may be needed. See LPV/r section.

Metabolism

- Metabolized by CYP450 (3A inducer); 80% excreted in urine (glucuronidated metabolites).
- **Dosing of NVP in patients with renal failure receiving hemodialysis:** An additional dose of NVP should be given following dialysis.
- **Dosing of NVP in patients with hepatic impairment:** NVP should not be administered to patients with moderate or severe hepatic impairment.

Drug Interactions (See also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.)***:***

- *Metabolism:* Nevirapine induces hepatic CYP450 including 3A (CYP3A) and 2B6; autoinduction of metabolism occurs in 2–4 weeks, with a 1.5–2-fold increase in clearance. There is potential for multiple drug interactions with nevirapine. Mutant alleles of CYP2B6 cause increases in nevirapine serum concentration in a similar manner but to a lesser extent than they do in efavirenz. Altered side effect profiles related to elevated nevirapine levels have not been documented probably because there are alternative CYP metabolic pathways for nevirapine[1]. (Please see efavirenz section for further details.)
- Before nevirapine is administered, the patient's medication profile should be carefully reviewed for potential drug interactions with nevirapine. Nevirapine should not be coadministered with atazanavir (with or without ritonavir).

Major Toxicities (Note that these toxicities are seen with continuous dosing regimens, not single-dose nevirapine prophylaxis):

- *More common:* Skin rash (some severe and requiring hospitalization; some life-threatening, including SJS and toxic epidermal necrolysis [TEN]), fever, nausea, headache, and abnormal hepatic transaminases. Nevirapine should be permanently discontinued and not restarted in children or adults who develop severe rash, rash with constitutional symptoms (i.e., fever, oral lesions, conjunctivitis, or blistering), or rash with elevated hepatic transaminases. Nevirapine-associated skin rash usually occurs within the first 6 weeks of therapy. If rash occurs during the initial 14-day lead-in period, do

not increase nevirapine dose until rash resolves. However, the risk of developing nevirapine resistance with extended lead-in dosing is unknown and is a concern that must be weighed against the patient's overall ability to tolerate the regimen and the current antiviral response.

- *Less common (more severe):* Severe, life-threatening, and in rare cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure (these are less common in children than adults). The majority of cases occur in the first 12 weeks of therapy and may be associated with rash or other signs or symptoms of HSR. Risk factors for nevirapine-related hepatic toxicity in adults include baseline elevation in serum transaminase levels, hepatitis B or C infection, female gender, and higher CD4 count at time of therapy initiation (CD4 count >250 cells/mm^3 in adult females and >400 cells/mm^3 in adult males). HSRs have been reported, including but not limited to severe rash or rash accompanied by fever, blisters, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise, and significant hepatic abnormalities. Nevirapine should be permanently discontinued and not restarted in children or adults who develop symptomatic hepatitis, severe transaminase elevations, or HSRs.

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/NVP.html).

Pediatric Use: Nevirapine is Food and Drug Administration (FDA) approved for use in children from infancy onward and remains a mainstay of therapy, especially in resource-limited settings. Nevirapine has been studied in HIV-infected children in combination with nucleoside reverse transcriptase inhibitors (NRTIs) or with NRTIs and a protease inhibitor (PI)[2-10].

In infants and children previously exposed to single-dose nevirapine for prevention of mother-to-child transmission (PMTCT), nevirapine-based antiretroviral therapy (ART) is less likely than lopinavir/ritonavir-based ART to control virus load. In a small, nonrandomized study in Botswana, 6-month virologic and immunologic responses were compared between 15 infants who were exposed to single-dose nevirapine and 15 who were not exposed who initiated nevirapine-based ART at a mean age of 8 months (range 2–33 months) in follow-up from a PMTCT study[11]. Only 34% of the infants with a history of nevirapine exposure had an undetectable viral load (<400 copies/mL) compared with 91% of the unexposed cohort. CD4 percentage was also significantly lower in the exposed group (23%) compared with the unexposed group (31%). In contrast, in a study in Uganda, in which children with single dose nevirapine exposure started nevirapine-based treatment at an older age of 1.6 years, there was no difference in response to therapy between children with and without prior single-dose nevirapine exposure[12]. In a large randomized clinical trial, P1060, 153 children (mean age 0.7 years) previously exposed to nevirapine for perinatal prophylaxis were treated with zidovudine plus lamivudine plus the randomized addition of nevirapine versus lopinavir/ritonavir. At 24 weeks post-randomization, 24% of children in the zidovudine/lamivudine/nevirapine arm reached a virologic endpoint (virologic failure defined as <1 $\log_{10}$ decrease in HIV RNA in Weeks 12–24 or HIV RNA >400 copies/mL at Week 24) compared with 7% in the zidovudine/lamivudine/lopinavir/ritonavir arm, $p = 0.0009$. When all primary endpoints were considered, including virologic failure, death, and treatment discontinuation, the PI arm remained superior because 40% of children in the nevirapine arm met a primary endpoint versus 22% for the lopinavir/ritonavir arm, $p = 0.027$[13]. A comparison study of nevirapine versus lopinavir/ritonavir in children 6–36 months of age not previously exposed to nevirapine has reported similar results, suggesting that lopinavir/ritonavir-based therapy is superior to nevirapine-based therapy for infants, regardless of past nevirapine exposure[14].

Body surface area has traditionally been used to guide nevirapine dosing for infants and young children. It is important to avoid underdosing of nevirapine because a single point mutation may confer NNRTI resistance to both nevirapine and efavirenz. Younger children (≤8 years of age) have higher apparent oral clearance of nevirapine than older children and require a higher dosage to achieve equivalent drug exposure compared with children >8 years of age[7-8]. For that reason, the recommended dosing of nevirapine for children younger than 8 years old is 200 mg/m^2 of body surface area per dose (maximum dose 200 mg) administered twice daily. For children 8 years or older, the recommended dose is 120 mg/m^2 of body surface area per dose (maximum dose 200 mg) administered twice daily. Some practitioners dose nevirapine at 150 mg/m^2 of body surface area every 12 hours (maximum of 200 mg per dose) regardless of age, as recommended in the FDA-approved product label.

Extended-release nevirapine (400-mg tablets) was approved by the FDA for use in adult patients based on two ongoing trials: VERxVE and TRANxITION. VERxVE enrolled treatment-naive adults who received 200 mg of immediate-release nevirapine for 14 days before commencing daily dosing of nevirapine extended release or standard twice-daily dosing of immediate-release tablets. A backbone of tenofovir and emtricitabine was used. TRANxITION enrolled patients already receiving full-dose immediate-release nevirapine and randomized them to receive the extended-release tablets or remain on their current nevirapine regimen. Both studies have shown equivalent efficacy, side effect, and CD4 profiles through 48 (VERxVE) and 24 weeks (TRANxITION)[15]. No data exist on the use of extended-release nevirapine in patients younger than 18 years of age.

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